Claim Rejection Under 35 USC §103

Claims 2-4, 14, 15, 49-52 and 60-61 and 70 as being obvious over Shepard et al. (April 2000) in view of Grovit-Ferbas et al.(July 2000)

The Examiner is respectfully requested to withdraw this rejection for the following reasons. Applicants respectfully point out that current claim 2 recites that the composition is suitable as a nucleic acid positive control. The application supports the use of the composition as a positive control material in amplification methods for the detection of microorganisms. The reason this composition can serve as a reliable positive control material is because the microorganisms are purified, their surface proteins covalently modified in such a way that the microorganism is rendered nonpathogenic and yet the nucleic acids are left intact enough so as to be amenable to amplification, and then suspended in liquid matrix comprising a biological fluid such that the composition can be used in parallel with a test sample for amplification reactions.

Shepard et al., (2000) is directed to quantitation of HIV-1 in biological fluids. This reference provides a sample of biological fluid containing the virus. However, it does not provide a composition for use as a positive control in amplification reactions comprising purified virus which has been rendered non-pathogenic by covalent linkage with a compound having functional groups, yet leaving its nucleic acids amenable to amplification. Further, it also does not provide that the virus is purified before suspension in a liquid matrix comprising a biological fluid.

With respect to Grovit-Ferbas (2000), it is not clear what the Examiner's argument is since the Examiner (on page 3 of the Office action, 4th paragraph) has only provided an incomplete sentence. If the Examiner intends to maintain this rejection, the Examiner is respectfully requested to provide a complete argument. Nevertheless, it is respectfully pointed out that the reference of Grovit Ferbas is directed to vaccine compositions and not positive controls for amplification reactions. The method of Grovit-Ferbas is directed to maintaining the integrity of surface antigens for the purposes of generating an immune response while reducing infectivity. The process is a combination of formaldehyde treatment and thermal treatment. Table 1 of this reference demonstrates that formaldehyde plus thermal treatment caused reduction in infectivity (at least 6.25 logs by 3 minutes), yet binding of CD4 to gp120 continued to rise from 3 to 30 minutes (figure 5). Formaldehyde treatment alone caused a

reduction in infectivity and yet only a 34% reduction in binding of gp120 was observed. (page 5805, lines 56-61). Thus, the data and teachings of Grovit-Ferbas suggest a reduction in infectivity without significantly affecting surface proteins. This would not suggest to one skilled in the art that the nucleic acids would be left intact enough so as to be amenable to amplification. Rather, it would be counter-intuitive and therefore unexpected that a virus can be modified with a cross-linking agent and yet sufficiently maintain the integrity of the nucleic acids so as to be amenable to amplification as claimed in the present claims.

The Examiner contends it would be obvious to modify the virus of Shepard et al. by inactivating by the chemical treatment of Grovit-Ferbas et al. However, it is respectfully pointed out that the sample of Shepard is not purified virus sample. Inactivating an unpurified virus-containing biological sample of Shepard by the chemical and thermal treatment method of Grovit-Ferbas would not provide for the composition of the present claim 2. Further, as mentioned above the emphasis in Grovit-Ferbas is on maintaining the integrity of surface proteins while reducing the infectivity. Therefore, the combination of Grovit-Ferbas with Shepard would not lead one skilled in the art to make the presently claimed composition.

It is noteworthy that under Materials and Method section on page 1415, Shepard et al. mention the use of Organon-Teknika NASBA assays and the Roche Amplicor HIV-1 Monitor assay, and also mention the use of controls. The controls included in the kits and are based on either armored RNA technology (Roche Monitor) or on purified RNA internal controls (NASBA). These controls are not whole virus preparations as claimed in the present claims. If, as the Examiner contends, it would have been obvious to prepare the composition of claim 2 which is suitable as a positive nucleic acid amplification control, one would expect Shepard et al. to have used such controls.

Thus, Applicants assert that the positive control composition of claim 2 was not even contemplated by Shepard et al. or Grovit-Ferbas et al. either alone on in combination. Applicants assert that contrary to the Examiner's assertions, there is no motivation for one skilled in the art to combine the references, and even if combined, such a combination would not lead to the composition of claim 2.

Applicants emphasize that the use of positive controls in nucleic acid amplification based methods for detecting the presence of microorganisms is critical for accurate results. The present composition can be used for this purpose because of the purification and suspension in

a liquid matrix comprising a biological fluid or a simulated biological fluid. Further, the composition as recited in claim 2, can be stored as 2-8°C (page 14, lines 29-30) and yet maintain its ability to serve as a positive control material. None of these features are contemplated in the cited references. Therefore, Applicants assert that the cited references do not teach, motivate or suggest a composition as recited in the amended claims.

Based on the above arguments, Applicants respectfully assert that the present compositions are not obvious in view of the cited references.

Claims 2-4, 14, 15, 49-52 and 60-61 and 70 as being obvious over Shepard et al. (April 2000) in view of Grovit-Ferbas et al., July 2000) and further in view of Norman et al. (1970)

The references of Shepard et al. and Grovit-Ferbas et al. have been discussed above. The reference of Norman et al. is directed to freezing of Mycoplasma. The stored mycoplasma can be thawed and then used for further studies. These microogansims were not rendered non-pathogenic. Upon reading Norman, one would be motivated to design compositions in which the microorgansism are still alive and not inactivated, which is in contrast to the current claims in which the microorgansism are purified, rendered non-pathogenic and yet amenable to nucleic acid amplification. Further, the suspension in sucrose solution as in Norman, is distinct from suspension of the purified inactivated virus in a liquid matrix comprising a biological fluid as recited in the current claim 2.

Therefore, Applicants respectfully assert that none of the references cited by the Examiner suggest or motivate the current composition which comprises: a purified microorganism which has been rendered non-pathogenic by covalent linkage of surface proteins and yet is amenable to nucleic acid amplification; and is suspended in a liquid matrix comprising a biological fluid such that it is suitable as a positive nucleic acid control.

Conclusion

Based on the amendments and the arguments presented herein, Applicants believe claims 2-9, 13-17, 49-57, 60-63 and 70 are now in a condition for allowance and therefore request the Examiner to allow these claims.

This response and RCE request is being filed with a request for a three month extension. Checks for $1020 (for the three month extension) and $790 (for the RCE) are enclosed. Any additional fee maybe charged to Deposit Account No. 08-2442.

Respectfully submitted,

By: _____
Ranjana Kadle, Reg. No. 40,041

HODGSON RUSS LLP
One M & T Plaza, Suite 2000
Buffalo, New York 14203-2391
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